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*Published in:*
HemaSphere

*DOI:*
10.1097/HS9.0000000000000370



*Publication date:*
2020

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Letter
OPEN ACCESS

# Carfilzomib Combined With Thalidomide and Low-dose Dexamethasone for Remission Induction and Consolidation in Newly Diagnosed Transplant Eligible Patients With Multiple Myeloma: 8 vs 4 Induction Cycles; the Carthadex Trial

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Survival in patients with multiple myeloma (MM) has significantly improved during the last decades due to the introduction of novel therapies. In transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) the depth of response following induction therapy is associated with a better progression free survival (PFS) and overall survival (OS).[1,2] However, it is currently unknown whether further improvement in response by increasing the number of induction cycles will translate in a better long-term outcome. Standard induction therapy consists of 4 to a maximum of six[3] cycles of treatment including a proteasome inhibitor, an immunomodulatory drug and dexamethasone. The paradigm that improvement in response that in general is observed with increasing number of induction cycles will lead to a better outcome might be false. To the best of our knowledge, data from randomized clinical trials are lacking. Therefore, we here describe the outcome of a cohort study in which cohorts were treated with either 4 or 8 induction cycles of KTd.

Widely accepted regimens are combinations of bortezomib, thalidomide and dexamethasone (VTd) or bortezomib, lenalidomide, and dexamethasone (VRd). Unfortunately, the combination of bortezomib and these Imids is associated with the occurrence of polyneuropathy (PNP), which may require dose reductions or early discontinuation of treatment.[4] Carfilzomib is a selective proteasome inhibitor that has irreversible binding to the 20S proteasome resulting in accumulation of the proteasome substrates. Previous trials showed that the incidence of PNP in patients treated with carfilzomib is lower than with bortezomib, which makes carfilzomib a good alternative for use in NDMM.[5,6]

In this single-arm, open-label, phase 2 dose escalation trial of the European Myeloma Network the combination of carfilzomib with thalidomide and dexamethasone (KTd) for induction and consolidation therapy was investigated in transplant eligible patients with NDMM. The results of 4 dose levels of carfilzomib (27, 36, 45, 56 mg/m$^2$) have recently been published.[6] Overall response rate (ORR) after induction therapy was 93% with a complete remission (CR) rate of 18%. ORR increased to 94% after consolidation therapy with a CR rate of 63%. Median PFS was 58 months and median OS was 83 months.[6] There were no significant differences in outcome between the dose levels of carfilzomib.

We here present the results of intensified induction with 8 cycles of KTd, and compared these data to the data we obtained from treatment with 4 cycles of KTd whereby carfilzomib was dosed twice weekly at 56 mg/m$^2$.

This is an open-label, phase 2 trial in which 20 patients dosed with 4 KTd induction cycles in the previous dose-escalation trial were compared with a new cohort of patients treated with 8 induction cycles.[6] Transplant eligible patients aged between 18 and 65 years with NDMM were included. Patients were treated with 4 or 8 cycles of KTd for induction, respectively. The dose of carfilzomib was 20 mg/m$^2$ i.v. on days 1and 2 followed by 56 mg/m$^2$ on days 8, 9, 15, and 16 of cycle 1 and on days 1, 2, 8, 9, 15,

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This trial was supported by funding from Onyx Pharmaceuticals, Inc., an Amgen subsidiary.
The authors have indicated that they have no potential conflicts of interest to disclose.

HemaSphere (2020) 4:4(e370). http://dx.doi.org/10.1097/HS9.0000000000000370.
Received: 25 February 2020 / Accepted: 9 March 2020

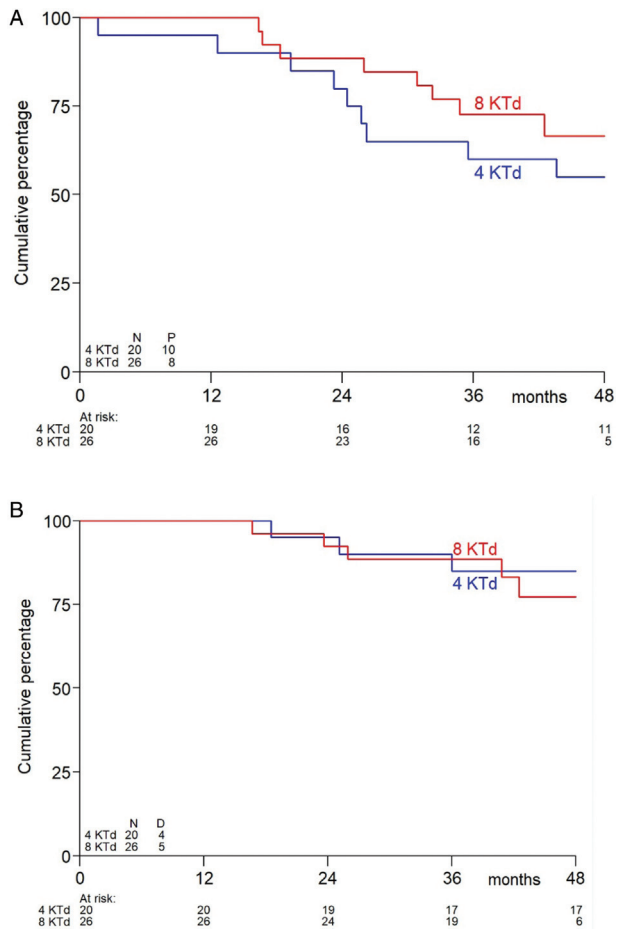


**Figure 1. A: Progression free survival, B: Overall survival.**

and 16 of cycles 2 to 4 or 2 to 8. Thalidomide dose was 200 mg orally on days 1 through 28 and dexamethasone dose was 40 mg orally on days 1, 8, 15, and 22 of a 28-day cycle. Induction therapy was followed by stem cell harvest after cyclophosphamide priming (2 mg/m$^2$) and daily 10 μg/kg granulocyte colony-stimulating factor. Hereafter, patients received HDM (200 mg/m$^2$) and ASCT followed by 4 consolidation cycles with KTd in the same schedule as during induction therapy except a lower dose of thalidomide (50 mg). The primary endpoint was response after induction therapy, specifically CR and very good partial response (VGPR). Secondary endpoints were efficacy and safety, PFS and OS.

For this prospective analysis, 46 eligible patients were analyzed, 26 patients were treated with 8 cycles of KTd induction therapy vs 20 patients treated with 4 cycles of KTd at carfilzomib 56 mg/m$^2$. Median age was 57 years [range 37–66 years]. ISS stages I/II/III/unknown were 43%/35%/20%/2%, respectively. A total of 50% of patients were classified as high risk based on cytogenetics and ISS stage; 33% of patients were classified as standard risk. In 17% of patients, risk status was unknown, mainly due to missing cytogenetics. Patients were considered to be high-risk if they had t(4;14) and/or del(17p) and/or add(1q) and/or ISS stage III.

Median follow-up was 51.4 months [range 33.3–74.1 months]. Response with 8 KTd and with 4 KTd after induction was ≥ CR in 27% vs 20%, ≥ VGPR in 92% vs 80% and ≥ PR in 96% vs 90%. Response with 8 KTd vs 4 KTd after HDM was CR in 35% vs 30%. After consolidation treatment CR rate increased to 58% vs 65%, respectively.

In patients treated with 8 KTd induction, PFS and OS at 48 months were 67% and 77% respectively, as compared with 55% and 85% after 4 KTd (Fig. 1).

Induction treatment with 8 KTd resulted in a higher incidence of premature discontinuation of carfilzomib (12%) and dexamethasone (12%) than with 4 KTd (5% and 5%, respectively) (Table 1). Reason for premature discontinuation were PNP (n = 3), anemia and fatigue (n = 1), skin toxicity (n = 1), progression of disease (n = 1). With 4 and 8 KTD median relative dose intensity of carfilzomib was 98% [IQR 92–100]. Seven patients (27%) completed 8 induction cycles without any reduction in dose level.

Grade 3 and 4 toxicity rates were higher with 8 KTd with respect to anemia, respiratory complications, polyneuropathy, and cardiac disorders. Cardiac events grade 3 and 4 in patients treated with 8 KTd occurred in 4 patients (15%, heart failure [2 patients] and hypertension [2 patients]). With 4 KTd heart failure grade 3 was reported in 1 patient (5%).

In conclusion, in this prospective, multicenter, non-randomized phase 2 trial, 8 cycles of KTd resulted in slightly higher percentages of CR and VGPR as compared to 4 KTd, with almost all patients achieving at least a PR. However, more cardiac events and premature discontinuation of treatment were observed. Moreover, response percentages after HDM/ASCT as well as after consolidation were comparable between the 2 groups and

**Table 1**

**Adherence to Treatment Protocol During Induction and Consolidation Between Dose Levels.**

| Column 1 | Induction 4 Induction Cycles at 56 mg/m$^2$ | 8 Induction Cycles at 56 mg/m$^2$ | Consolidation 4 Induction Cycles at 56 mg/m$^2$ | 8 Induction Cycles at 56 mg/m$^2$ |
|---|---|---|---|---|
| Patients, n | 20 | 26 | 19 | 22 |
| Carfilzomib | | | | |
| Normal completion | 15 (75) | 10 (38) | 10 (53) | 10 (45) |
| Dose delay, reduction and/or interruption | 4 (20) | 13 (50) | 4 (21) | 6 (27) |
| Premature stop | 1 (5) | 3 (12) | 5 (26) | 6 (27) |
| Thalidomide | | | | |
| Normal completion | 7 (35) | 7 (27) | 7 (37) | 9 (41) |
| Dose delay, reduction and/or interruption | 10 (50) | 16 (62) | 3 (16) | 3 (14) |
| Premature stop | 3 (15) | 3 (12) | 9 (47) | 10 (45) |
| Dexamethasone | | | | |
| Normal completion | 14 (70) | 13 (50) | 11 (58) | 10 (45) |
| Dose delay, reduction and/or interruption | 5 (25) | 10 (38) | 3 (16) | 5 (23) |
| Premature stop | 1 (5) | 3 (12) | 5 (26) | 7 (32) |

more importantly, also PFS and OS were not different. A limitation of our study is that we used cohorts of patients instead of a randomization. Moreover, we choose a regimen that is less feasible with only 38% of patients being treated as planned. As a consequence, the improvement in response was limited. Therefore, we cannot define whether increasing response with additional cycles of therapy will translate in a better (progression free) survival or indicates more refractory disease with inferior outcome.

Our data do not support lengthening induction therapy with KTd, as the increase in response is limited and does not translate in an improvement in PFS and OS. Moreover, feasibility was modest with only 38% of patients receiving full dose in time. Therefore we conclude that in transplant-eligible NDMM 4 induction cycles should remain the standard.

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